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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
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16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/614,505	Applicant(s) ROTHBERG ET AL.	
	Examiner Janell Cleveland Taylor	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

The following Office Action is **FINAL**, necessitated by the amendment filed July 20, 2001 (paper # 10). Any rejection not reiterated is withdrawn. The previous Office Action, dated 9/21/01 (paper #12) did not contain a complete response to Applicant's arguments, and therefore they are addressed below. Also, although another reference is used below in the U.S.C. 103(a) rejection of claims 27-42 and 47-57, which was not used in the final rejection of paper # 12. However, had this reference been used in paper #12, the action still would have been made final as the amendment of paper #10 necessitated this rejection.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 27-42 and 47-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb et al. (USPN 6,060,240) in view of Short et al. (USPN 6,174,673) and further in view of Okayama (Molecular and Cellular Biology, Vol. 2, No.2, pages 161-170).

Kamb et al. teaches "Gene libraries, usually cDNA or genomic, can be constructed in a variety of vectors including plasmid and viral vectors by methods well-established in the art. See, among other references, Sambrook et al., supra. The library vectors can be designed to propagate on one or more of a variety of cell types

including bacteria, yeast, or mammalian cells. In some cases the libraries are intended to be as representative of the nucleic acids present in a particular organism or tissue as possible. These are termed total genomic or cDNA libraries. In other cases the libraries are intended to contain only a subset of sequences; for example, those sequences that are prevalent in one cell type and absent in another. Such limited libraries can be constructed using, for example, cDNA from one source that has been treated with subtraction or blocking procedures as suggested above to remove sequences held in common with a second source. See, supra. Libraries have traditionally been used in two ways: for biochemical screens and for genetic screens. The process of screening allows isolation of sequences of interest from the bulk of library sequences. Biochemical screens require a probe, either a nucleic acid probe or a protein probe such as an antibody (in the case of expression libraries). Specific genes or gene fragments can be fished out of a library using an appropriate probe. Genetic screens permit recovery of sequences from a library of genes or gene fragments which complement or rescue a particular mutant phenotype using an appropriate selection scheme. For example, if a yeast genomic library is introduced into HIS3-yeast cells and plated on media lacking histidine, only cells that have acquired library sequences that contain a functional HIS3 gene will be able to grow. These growing colonies can be treated such that the resident library sequences are recovered. A number of ways can be envisioned to enrich and identify differentially expressed library members. For example, Representational Difference Analysis (RDA) permits the purification of sequences that differ substantially

between two samples because, e.g., they contain a restriction fragment length polymorphism." (Cols. 26 and 27).

Kamb does not teach fractionating the set as well as the subset.

Short teaches "One embodiment for forming a normalized library from an environmental sample begins with the isolation of nucleic acid from the sample. This nucleic acid can then be fractionated prior to normalization to increase the chances of cloning DNA from minor species from the pool of organisms sampled. DNA can be fractionated using a density centrifugation technique, such as a cesium-chloride gradient. When an intercalating agent, such as bis-benzimide is employed to change the buoyant density of the nucleic acid, gradients will fractionate the DNA based on relative base content. Nucleic acid from multiple organisms can be separated in this manner, and this technique can be used to fractionate complex mixtures of genomes. This can be of particular value when working with complex environmental samples. Alternatively, the DNA does not have to be fractionated prior to normalization. Samples are recovered from the fractionated DNA, and the strands of nucleic acid are then melted and allowed to selectively reanneal under fixed conditions... When a mixture of nucleic acid fragments is melted and allowed to reanneal under stringent conditions, the common sequences find their complementary strands faster than the rare sequences. After an optional single-stranded nucleic acid isolation step, single-stranded nucleic acid representing an enrichment of rare sequences is amplified using techniques well known in the art, such as a polymerase chain reaction...and used to generate gene libraries. This procedure leads to the amplification of rare or low abundance nucleic acid

molecules, which are then used to generate a gene library which can be screened for a desired bioactivity. While DNA will be recovered, the identification of the organism(s) originally containing the DNA may be lost. This method offers the ability to recover DNA from "unclonable" sources." (Col. 13).

It would have been obvious to one of ordinary skill in the art at the time of the invention to fractionate both the set and the subset of nucleic acid. This is because, as Short teaches, "Nucleic acid from multiple organisms can be separated in this manner, and this technique can be used to fractionate complex mixtures of genomes. This can be of particular value when working with complex environmental samples." That would apply to any complex sample, not just environmental samples. Also, as Short points out, this technique would have led to amplification of rare or low abundance nucleic acid molecules, which can then be used in the gene library. It also would have been obvious to one of ordinary skill that it would have been beneficial to fractionate and recover a sample first from a genomic pool, which would have allowed for a specific chromosome, chromosome fragment, or gene to be separated. Secondly, it would have been obvious to then create a library from this population and then fractionate this population, recover a subset, and isolate and sequence it. This would have been obvious because it would have allowed one of ordinary skill in the art to further purify and distinguish specific genes or regions within a gene, which would have been impossible to fractionate from an entire genomic population because the entire population would have been too large to allow for smaller sections to be isolated.

Neither Kamb nor Short teaches sequencing the fragment after recovery, or the use of gel electrophoresis to separate the fragments based on size.

Okayama et al. teaches using gel electrophoresis to separate the various sizes, and DNA sequencing of the sequences after being in the library. (Page 164, second column).

It would have been obvious to one of ordinary skill in the art at the time of the invention to sequence the fragments after recovery, or to run them in a gel and discriminate between them based on size. This is because these additional methods would have provided the actual sequence information, which would have been helpful in determining the origin and usefulness of that individual sequence.

3. Claims 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb et al in view of Short in view of Okayama as applied to claims above, and further in view of Macevicz et al. (USPN 6,136,537).

As disclosed above, Kamb et al. teaches ""Gene libraries, usually cDNA or genomic, can be constructed in a variety of vectors including plasmid and viral vectors by methods well-established in the art. See, among other references, Sambrook et al., supra. The library vectors can be designed to propagate on one or more of a variety of cell types including bacteria, yeast, or mammalian cells. In some cases the libraries are intended to be as representative of the nucleic acids present in a particular organism or tissue as possible. These are termed total genomic or cDNA libraries. In other cases the libraries are intended to contain only a subset of sequences; for example, those sequences that are prevalent in one cell type and absent in another. Such limited

libraries can be constructed using, for example, cDNA from one source that has been treated with subtraction or blocking procedures as suggested above to remove sequences held in common with a second source. See, supra. Libraries have traditionally been used in two ways: for biochemical screens and for genetic screens. The process of screening allows isolation of sequences of interest from the bulk of library sequences. Biochemical screens require a probe, either a nucleic acid probe or a protein probe such as an antibody (in the case of expression libraries). Specific genes or gene fragments can be fished out of a library using an appropriate probe. Genetic screens permit recovery of sequences from a library of genes or gene fragments which complement or rescue a particular mutant phenotype using an appropriate selection scheme. For example, if a yeast genomic library is introduced into HIS3-yeast cells and plated on media lacking histidine, only cells that have acquired library sequences that contain a functional HIS3 gene will be able to grow. These growing colonies can be treated such that the resident library sequences are recovered. A number of ways can be envisioned to enrich and identify differentially expressed library members. For example, Representational Difference Analysis (RDA) permits the purification of sequences that differ substantially between two samples because, e.g., they contain a restriction fragment length polymorphism." (Cols. 26 and 27).

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minor species from the pool of organisms sampled. DNA can be fractionated using a density centrifugation technique, such as a cesium-chloride gradient. When an intercalating agent, such as bis-benzimide is employed to change the buoyant density of the nucleic acid, gradients will fractionate the DNA based on relative base content. Nucleic acid from multiple organisms can be separated in this manner, and this technique can be used to fractionate complex mixtures of genomes. This can be of particular value when working with complex environmental samples. Alternatively, the DNA does not have to be fractionated prior to normalization. Samples are recovered from the fractionated DNA, and the strands of nucleic acid are then melted and allowed to selectively reanneal under fixed conditions... When a mixture of nucleic acid fragments is melted and allowed to reanneal under stringent conditions, the common sequences find their complementary strands faster than the rare sequences. After an optional single-stranded nucleic acid isolation step, single-stranded nucleic acid representing an enrichment of rare sequences is amplified using techniques well known in the art, such as a polymerase chain reaction...and used to generate gene libraries. This procedure leads to the amplification of rare or low abundance nucleic acid molecules, which are then used to generate a gene library which can be screened for a desired bioactivity. While DNA will be recovered, the identification of the organism(s) originally containing the DNA may be lost. This method offers the ability to recover DNA from "unclonable" sources." (Col. 13).

It would have been obvious to one of ordinary skill in the art at the time of the invention to fractionate both the set and the subset of nucleic acid. This is because, as

Short teaches, "Nucleic acid from multiple organisms can be separated in this manner, and this technique can be used to fractionate complex mixtures of genomes. This can be of particular value when working with complex environmental samples." That would apply to any complex sample, not just environmental samples. Also, as Short points out, this technique would have led to amplification of rare or low abundance nucleic acid molecules, which can then be used in the gene library. It also would have been obvious to one of ordinary skill that it would have been beneficial to fractionate and recover a sample first from a genomic pool, which would have allowed for a specific chromosome, chromosome fragment, or gene to be separated. Secondly, it would have been obvious to then create a library from this population and then fractionate this population, recover a subset, and isolate and sequence it. This would have been obvious because it would have allowed one of ordinary skill in the art to further purify and distinguish specific genes or regions within a gene, which would have been impossible to fractionate from an entire genomic population because the entire population would have been too large to allow for smaller sections to be isolated.

Neither Kamb nor Short teaches sequencing the fragment after recovery, or the use of gel electrophoresis to separate the fragments based on size.

Okayama et al. teaches using gel electrophoresis to separate the various sizes, and DNA sequencing of the sequences after being in the library. (Page 164, second column).

It would have been obvious to one of ordinary skill in the art at the time of the invention to sequence the fragments after recovery, or to run them in a gel and

discriminate between them based on size. This is because these additional methods would have provided the actual sequence information, which would have been helpful in determining the origin and usefulness of that individual sequence. Furthermore, normalizing would have been obvious because it would have allowed for underrepresented members of the mRNA population to be sequenced.

Neither Kamb nor Okayama et al. nor Short teaches the use of a restriction endonuclease that is a Type II or IIS, or the terminal sequences of the nucleic acids.

Macevicz et al. teaches that "Preferably, the method of the invention comprises the steps of i) providing a population of polynucleotides having predetermined ends; ii) inserting each polynucleotide of the population into a vector, so that the vector has at least one type IIs restriction endonuclease recognition site adjacent to each end of the inserted polynucleotide, each type IIs restriction endonuclease recognition site being oriented such that a type IIs restriction endonuclease recognizing either site cleaves the vector interior to the inserted polynucleotide; iii) cleaving each vector with one or more type IIs restriction endonucleases recognizing the type IIs restriction endonuclease recognition sites so that the vector is linearized and has a sequence tag of the inserted polynucleotide at each end; iv) re-circularizing the vector to form a pair of sequence tags for the inserted polynucleotide; and v) determining the nucleotide sequence of each pair of sequence tags of a sample of re-circularized vectors. Preferably, the population of polynucleotides having predetermined ends is produced by digesting a cDNA library with one or more frequent-cutting restriction endonucleases, e.g. restriction endonucleases each having a four-base recognition sequences. Preferably,

the pairs of sequence tags are tabulated to form a frequency distribution of sequences in the population of polynucleotides which may be used directly, or related to the frequency distribution of sequences in another population, such as a cDNA library, from which the analyzed population is derived. In one aspect of the invention, the pairs of sequence tags are excised from the re-circularized vectors and ligated together to form a concatemers, which are cloned in a conventional sequencing vector." (Col. 2, lines 32-65).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Macevicz et al. to excise certain portions of the nucleic acid from the vector library. This is because it would have allowed for specific sequences to be isolated, purified, and sequenced.

Summary

4. Claims 27-57 are rejected under 35 U.S.C. 103(a).

Response to Arguments

5. Applicant's arguments filed April 1, 2002 have been fully considered but they are not persuasive. First of all, Applicant argues that their arguments were not clearly addressed in paper #12. Examiner offers her apology for this, and herein addresses all arguments presented in the Response pursuant to the Notice of Appeal, paper #14.

On page 3, second paragraph of Applicant's response, and on page 3, last paragraph, bridging page 4, through the 3rd paragraph of page 4, it is argued that Neither Kamb nor Okayama teach two fractionation steps. However, this argument has been obviated by the addition of a third reference, Short. Furthermore, as detailed

above, it would have been obvious to use two fractionation steps because it would have been obvious to further purify and distinguish specific genes or regions within a gene, which would have been impossible to fractionate from an entire genomic population because the entire population would have been too large to allow for smaller sections to be isolated.

Next, on page 3, 3rd and 4th paragraphs, as well as on page 6, 3rd and 4th paragraphs, Applicant argues that Kamb, as well as Macevicz, when considered as a whole, addresses a different problem from that of the present invention. It is argued that Kamb relates to a method for the comparative assessment of the level of specific nucleic acid sequences in samples derived from different sources. However, limitations cannot be read into a claim which do not exist. The claims are drawn to identifying a nucleic acid sequence, and Kamb also teaches identifying a nucleic acid sequence. (Col. 27, lines 6-10). The claim does not include the limitation that the nucleic acid is unknown, and even if it did, the method steps would still be obvious because the art is analogous in the sense that it is in the same class and subclass, and addresses gene libraries in which a specific gene or gene fragment may be fished out. In Col. 25, line 53, Kamb teaches "This approach provides the means to identify specific sequences that are selectively lost from a library..." Furthermore, Applicant states that Kamb teaches the use of at least two independent cell types rather than the single vector claimed in the instant application. However, there are no limitations found in the claims that state that one and only one vector may be used. Kamb teaches a comparative

assay, and therefore uses different vectors. The method of using a single vector remains obvious, however, as discussed above.

Applicant also states that "rather than urging the use of RDA, Kamb teaches away from this process." However, Kamb merely states that this method is known to have limitations. Kamb does not teach that the method would not work or has not been used. To the contrary, Kamb teaches that the method is broadly used and even gives an example of its use. To be obvious, a reference does not need to show that the method would have been the best possible means known in the art at that time. It need only teach that it was known, and was used, which the Kamb reference accomplishes. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (See MPEP 2145).

It is argued on page 6 that Macevicz teaches a process step for recircularizing an insertion-vector. However, as part of the overall invention of Macevicz, a step of producing a cDNA library with one or more frequent-cutting restriction enzymes is taught (Col. 2, lines 55-60). Therefore, the art is analogous because both methods use a library and must excise the material therein.

In regards to Applicant's argument that the references used are related to different problems than that solved by the method of the instant claims, MPEP Section

2141 states that "The examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." Clearly in this case the art of Kamb, Okayama, Short, and Macevicz is all analogous because they all seek to solve the problem of identifying or isolating nucleic acids. See In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). See also In re Deminski, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986); In re Clay, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) ("A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); and Wang Laboratories Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993). The art used in the above action would have logically commended itself to each other because each deals with a similar problem, that of dealing with nucleic acids.

The MPEP, section 2141, also states that "PTO classification is some evidence of analogy but similarities and differences in structure and function carry more weight." All of the references used reside in the same class and subclass that the instant application is placed in. In regards to the chemical arts, the MPEP gives, for example, Ex parte Bland, 3 USPQ2d 1103 (Bd. Pat App. & Inter. 1986) (Claims were drawn to a particulate composition useful as a preservative for an animal foodstuff (or a method of

inhibiting fungus growth in an animal foodstuff therewith) comprising verxite having absorbed thereon propionic acid. All references were concerned with absorbing biologically active materials on carriers, and therefore the teachings in each of the various references would have been pertinent to the problems in the other references and the invention at hand.); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983) (Problem confronting inventor was preventing electrostatic buildup in PTFE tubing caused by hydrocarbon fuel flow while precluding leakage of fuel. Two prior art references relied upon were in the rubber hose art, both referencing the problem of electrostatic buildup caused by fuel flow. The court found that because PTFE and rubber are used by the same hose manufacturers and experience the same and similar problems, a solution found for a problem experienced with either PTFE or rubber hosing would be looked to when facing a problem with the other.); In re Mlot-Fijalkowski, 676 F.2d 666, 213 USPQ 713 (CCPA 1982) (Problem faced by appellant was enhancement and immobilization of dye penetrant indications. References which taught the use of dyes and finely divided developer materials to produce colored images preferably in, but not limited to, the duplicating paper art were properly relied upon because the court found that appellant's problem was one of dye chemistry, and a search for its solution would include the dye arts in general.) The examples given are clear indications that the art is analogous. All deal with the problem of nucleic acids, which are analogous by structure and function.

On page 4, 1st paragraph, Applicant states that there is no support provided for the assertion that it would have been obvious to one of ordinary skill in the art to

fractionate both the set and the subset. However, as argued above, it would have been obvious to create a library from this population and then fractionate this population, recover a subset, and isolate and sequence it. This would have been obvious because it would have allowed one of ordinary skill in the art to further purify and distinguish specific genes or regions within a gene, which would have been impossible to fractionate from an entire genomic population because the entire population would have been too large to allow for smaller sections to be isolated. It would have been obvious to fractionate a subset for the same reasons that it would have been to fractionate the first set. This is because the same motivation exists for doing it the second time as it did the first, as individual nucleic acid segments may be identified in this manner.

On page 4, 2nd paragraph, and on page 6, 5th paragraph, Applicant argues that the combination of the references would have constituted impermissible hindsight. However, "[a]ny judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re McLaughlin 443 F.2d. (See also MPEP section 2145). The art used in the above rejections takes into account the level of one of ordinary skill in the art. It does not include knowledge gleaned only from applicant's disclosure, but from what would have been obvious to one of ordinary skill in the art.

Next, on page 5, first full paragraph, Applicant argues that the reference of Okayama does not overcome the deficiencies of Kamb because Okayama teaches that

"non nucleases" are used in the process. However, this is the reason that the Macevicz reference was used for claims 43-46. Furthermore, Okayama was used to show gel electrophoresis and sequencing are obvious, and did not attempt to address the cloning step, which was found in the Kamb reference. Okayama was used only to show sequencing and electrophoresis, both which occur after the cloning step.
Applicant argues in the 2nd paragraph of page 5 that there must be some suggestion or motivation for combining the reference of Okayama and Kamb. This is given above in the paragraph following the outline of what both references teach. To reiterate, it would have been obvious to one of ordinary skill in the art at the time of the invention to sequence the fragments after recovery, or to run them in a gel and discriminate between them based on size. This is because these additional methods would have provided the actual sequence information, which would have been helpful in determining the origin and usefulness of that individual sequence.

Applicant also argues on page 5, 3rd paragraph, that additional limitations found in claims 38-42, 50, 53, and 57 are not addressed. The limitation of claims 38-42 is that members of a set differ from each other by a specified length. Since, however, Applicant has not define "set" as any particular gene or size of fragment, the "set" may in fact be identical nucleic acids cloned into different vectors. Because the "set" comes from a population, one of ordinary skill in the art would have known that the set would have been the same fragments. Claim 50 recites that the two or more member nucleic acids are pooled prior to fractionating. Since all of the nucleic acid molecules being pooled were from a library, and since more than one host may act as a vector, the

nucleic acids would have been pooled when they were fractionated from the library. The limitations of claim 53 are those of a standard gel electrophoresis, as found in the reference of Okayama. (Page 164, 2nd column.) Claim 57 teaches that the fractionating further comprises multiplexing a plurality of recovered nucleic acids, but as pointed out in regards to claim 50 above, multiplexing, as well as pooling, would have occurred as part of the fractionation from the library anyway, because the nucleic acids would have been in different vectors and would have "pooled" or "multiplexed" as a result of their fractionation.

Lastly, on page 7, Applicant argues that there is no suggestion or motivation for combining the art of Kamb and Okayama with that of Macevicz. Applicant states that no basis for modifying Kamb and Okayama, or for combining their teachings with Macevicz, are given. However, as stated above, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Macevicz et al. to excise certain portions of the nucleic acid from the vector library. This is because it would have allowed for specific sequences to be isolated, purified, and sequenced.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 305-3014 or 305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

April 5, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600